REMARKS

Status Summary

Claims 44-46 and 49-55 are pending. Claims 44-46, 49, and 51-53 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Cobbold et al. (U.S. Patent No. 6, 056,956) in view of Lederman et al. (U.S. Patent No. 5,474,771) or Armitage et al. (U.S. Patent No. 6,087,329). Claims 50, 54, and 55 are rejected under § 103(a) based on the above-cited references and further in view of Ramanathan et al. (WO 91/09059). Claims 44-46 and 49-55 further stand rejected under the judicially created doctrine of obviousness-type double patenting as unpatentable over claims 1-17 of U.S. Patent No. 5,942,229. Reconsideration in view of the following remarks is respectfully requested.

Rejection of Claims Under 35 U.S.C. § 103(a)
Based on Cobbold in view of Lederman or Armitage

Claims 44-46, 49, and 51-53 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Cobbold et al. (U.S. Patent No. 6, 056,956) in view of Lederman et al. (U.S. Patent No. 5,474,771) or Armitage et al. (U.S. Patent No. 6,087,329). The examiner's stated rationale for the rejection of claims under § 103(a) is essentially as set forth in prior Office Actions. In the view of the examiner, immunosuppression using anti-CD4 antibodies is allegedly extrapolated to the use of gp39 antagonists because both target CD4 T helper cells. This rejection is traversed for the reasons set forth below. The applicants respectfully traverse.

The examiner bears the burden of presenting a *prima facie* case for obviousness, with a showing of such *prima facie* obviousness requiring: (1) some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) the teaching or suggestion of all the claim limitations of the applicant's invention in the combined prior art references; and (3) a reasonable expectation of success. MPEP § 2143. Applicants respond that the examiner has failed to meet this burden.

With regard to the first of these factors, suggestion or motivation to combine, such motivation may be found "where there is some teaching, suggestion, or motivation ... either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art." MPEP § 2143.01 (citing *In re Kotzab*, 217 F.3d 1365, 1370

55 USPQ2d 1313, 1317 (Fed. Cir. 2000)). Not only must such motivation be present, "there must be some teaching, suggestion or motivation in the prior art to make the specific combination that was made by the applicant." *In re Dance,* 160 F.3d 1339, 1343, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998) (emphasis added) (citing *In re Raynes,* 7 F.3d 1037, 1039, 28 USPQ2d 1630, 1631 (Fed. Cir. 1993); *In re Oetiker,* 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992).

The fact that the prior art teaches individual elements of the claimed invention that are generally known or within the capabilities of one with knowledge in the art is not, however, sufficient to establish a *prima facie* case of obviousness without any specific teaching or suggestion for making the combination. Accordingly, in a proper analysis of obviousness, the level of knowledge of one with ordinary skill in the art cannot be substituted for a clear suggestion to make a combination. *See A-Site Corp. v. VSI International Inc.,* 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999).

Therefore, the examiner is required to show how and why the applicant would have been motivated to combine the references in the manner combined by the examiner. The examiner has not done so, but has simply made unsupported statements regarding the alleged motivation of a person of ordinary skill in the art to undertake the components of the claimed invention. When considered in combination, the Cobbold, Lederman, and Armitage lack any teaching, suggestion or motivation to make the specific combination of the presently claimed invention. Thus, applicants submit that the examiner has failed to meet the burden of establishing a *primae facie* case.

Cobbold describes methods for tolerance induction using nondepleting CD4 and CD8 antibodies. However, Cobbold states that "the mechanism(s) by which CD4 mAbs produce these effects are still not clear" (col. 1, lines 35-36). Thus, Cobbold neither states nor suggests that the use of any antibody that binds to a T helper cell antigen can be used to elicit tolerance. Indeed, Cobbold does not even attribute the success of their methods to interference with T helper cells.

Following a review of Cobbold, one skilled in the art would not surmise that the use of any antibody that binds to a T helper cell antigen can be used to induce tolerance. CD4 is expressed on T cells and monocytes/macrophages, natural killer lymphocytes, CD34+ progenitor cells and a subset of eosinophils and basophils. *See e.g.*, Biswas et al. (2003) *Blood* [Jan 16, electronic publication ahead of print]. Thus, the activity of anti-CD4

antibodies in inducing tolerance could potentially occur via interaction with one or more of these cells types. As stated by Cobbold, the mechanism of activity of anti-CD4 antibodies is unknown (col. 1, lines 35-36).

Lederman and Armitage teach that various immune responses can be inhibited using 5C8-specific antibodies (Lederman), which bind to an antigen on CD4 T cells, or CD40 antagonists (Armitage), which bind to the CD40 antigen on B cells. Neither Lederman nor Armitage teach induction of tolerance.

In rejecting the claims under § 103(a), the examiner states that "one of ordinary skill in the art at the time the invention was made would have been motivated to substitute these antagonists into the methods of Cobbold to similarly target T helper cells to inhibit humoral response to thymus-dependent antigens." Specifically, the examiner's finding of motivation relies on: (1) the CD4 T cell binding or "target[ing]" activity of the antagonists described in the cited references, and/or (2) a contention that long term unresponsiveness is expected based on achievement of initial unresponsiveness. Office Action, page 4.

The present invention provides that the activity of anti-gp39 antibodies in inducing prolonged humoral suppression lies in the inhibition of gp39 interaction with CD40 to thereby activate B cells, not an ability to bind to CD4 T helper cells. The cited references do not provide a specific suggestion to employ anti-gp39 antibodies, which have a specific role in inhibiting the interaction between gp39 and CD40, thereby induce tolerance. Contrary to the assertion of the examiner, an ability to "target" helper T cells is not equivalent to inhibition of humoral immunity. According to the examiner's rationale, any antibody that binds to a helper T cell antigen would be anticipated to have immunosuppressive activity. This conclusion is clearly in err. If one relies on the alleged motivation of the cited references, the resultant method is inoperable for many antibodies used to perform the method.

One skilled in the art would not anticipate that antibody targeting of a helper T cell would inevitably induce T cell tolerance. Targeting of T cells can activate, block tolerance, or actively prevent the induction of tolerance. For example, administration of anti-CD3 antibodies activates T cells by binding the T cell receptor. *See* Neumann et al. (1992) *Int J Immunopharmacol* 14:1295-9304; Urba et al. (1992) *Cancer Res* 52:2394-2401; Reid et al. (1992) *J Immunol* 148:2630-2635; Jamali et al. (1992) *J Immunol* 148:1613-1619; Yoshizawa et al. (1992) *Cancer Res* 52:1129-1136; Bluestone et al. (1992) *Int J Cancer Suppl* 7:39-41; Newell et al. (1991) *Ann N Y Acad Sci* 636:279-287; Ferran et al. (1991) *Clin Exp Immunol*

86:537-543; Demanet et al. (1991) *J Immunol* 147:1091-1097; Loeffler et al. (1991) *Cancer Res* 51:2127-2132; Chatenoud et al. (1991) *Curr Top Microbiol Immunol* 174:121-134; Ferran et al. (1990) *Transplant Proc* 22:1922-1923; Flamand et al. (1990) *J Immunol* 144:2875-2882. In contrast, administration of monoclonal antibodies that bind the T cell antigen CD28 blocks the induction of T cell tolerance. *See* Harding et al. (1992) *Nature* 356:607-609. As yet another possibility, administration of monoclonal anti-OX22 antibodies, which bind to CD+ T cells, exacerbates autoimmune disease. *See* Mathieson et al. (1993) *J Exp Med* 177:1309-1316. In addition, antibodies having a same binding specificity can be different in their capacity for cell depletion and tolerance induction (*i.e.*, the method of Cobbold requires the use of non-depleting antibodies). Thus, a skilled artisan could not reasonably predict which antibodies among those that target T cells would be effective in eliciting long term suppression of humoral immunity as recited in the pending claims.

Applicant further submits that the examiner's suggestion that an antibody as described by Lederman or by Armitage, or as disclosed in the present application, can be employed in the methods of Cobbold is inconsistent with the examiner's statements on the unpredictability of developing immunosuppressive therapies. Office Action, page 3. In support thereof, the examiner cites Auchincloss, (chapter 11 in Transplantation Immunology, Bach and Auchincloss Eds. Wiley-Liss, New York, 1995, pages 211-218). Applicant presumes, however, the examiner was instead referring to Strom & Suthanthiran (1996) in Austen et al. (eds), Therapeutic Immunology, Blackwell Science, Cambridge, Massachusetts, pp. 451-456, which is cited on the accompanying Notice of References Cited. Strom & Suthanthiran, which describes numerous ways in which immune responses can be suppressed, is consistent with the examiner's comments that, at the time of the instant invention, methods for inducing tolerance were unpredictable. The cited reference is also consistent with the teachings of Schonrich and Schneider, which were submitted with applicant's Response of October 25, 2002.

The unpredictability of methods for inducing tolerance is relevant to the patentability of pending claims, which are directed to the induction of tolerance. The examiner states that the pending claims do not recite tolerance. Office Action, page 3. The examiner also defines tolerance as the "long-lasting nonreactivity of the immune system to a specific set [of] antigens, maintained without on-going immunosuppression." Office Action, page 3. Applicants respectfully submit that "prolonged humoral immune suppression," as recited in

claim 44, is one aspect of tolerance. Specifically, claim 44 recites that "prolonged humoral immune suppression means that antibody production remains suppressed after the anti-gp39 antibody has been cleared from the subject." Claims 45-46, 49, and 51-53 ultimately depend from claim 44, and thus also include the element of prolonged humoral immune suppression.

The examiner also contends that long term unresponsiveness is expected based on achievement of initial unresponsiveness, which is described in the art. Specifically, the examiner suggests that the teachings of Armitage and Lederman, which are limited to transient inhibition of immune response and which do not describe tolerance induction, can be expected to also elicit prolonged immune responses. Office Action, page 4. Applicant respectfully submits that the examiner's contention is unsupported and is also inconsistent with the acknowledged unpredictability in the art of developing immunosuppressive therapies. In addition, existing immunosuppressive agents are known to induce transient immunosuppression but to prevent immune tolerance. For example, CsA paradoxically both blocks and enhances immune responses (Prud'homme et al., 1993), and specifically prevents induction of peripheral allograft tolerance (Li et al., 1999).

Based on the foregoing arguments, applicant believes that claims 44-46, 49, and 51-53 are unobvious over the cited references in accordance with 35 U.S.C. § 103(a) and that the examiner has failed to make a *primae facie* case of obviousness. Thus, applicant respectfully requests that the withdrawal of the rejection of claims 44-46, 49, and 51-53 under 103(a) be withdrawn.

Rejection of Claims Under 35 U.S.C. § 103(a)
Based on Cobbold, Lederman, and Armitage
and further in view of Ramanathan

Claims 50, 54, 55 are also rejected under § 103(a) based on the foregoing reasons and further in view of Ramanathan et al. (WO 91/09059). The examiner's rationale for also relies on In re Kerkhoven, which held that preparation of a composition is obvious when prepared by combination of two compositions which are individually useful for the same purpose. This rejection is respectfully traversed.

Initially, applicants respond that the combined teachings of Cobbold, Armitage, and Lederman, do not render obvious the methods of the present invention as described herein above. Specifically, the combined teachings fail to teach, suggest or motivate that anti-gp39 antibodies can induce tolerance as recited in the pending claims. Ramanathan describes the

use of IL-4 antagonists to inhibit allergic responses. This disclosure does not cure the deficiency of Cobbold, Armitage, and Lederman because it similarly does not teach, suggest or motivate that anti-gp39 antibodies can induce tolerance.

Applicants further respond that In re Kerkhoven does not bear on the present case because the pending claims are directed to methods rather than compositions as in Kerkhoven. A combination in accordance with Kerkhoven required no more than mixing of two known compounds. In contrast, significant challenges exist in developing combination therapies, particularly immunosuppression therapies that pose risks of infection. For example, when developing combination therapies to prevent transplant rejection, an important immunological consideration is appropriate reduction or withdrawal of an immunosuppressive drug when that toxic responses exceed therapeutic benefits. *See e.g.*, Strom & Suthanthiran, page 451, col. 2. As stated herein above, the unpredictability of methods for inducing tolerance support the unobviousness of the present invention.

Based on the foregoing arguments, applicant believes that claims 50, 54, and 55 are unobvious over the cited references, including Ramanathan. Thus, applicant respectfully requests that the withdrawal of the rejection of claims 50, 54, and 55 under 35 U.S.C. § 103(a) be withdrawn.

Rejection of Claims Based on Non-Statutory
Obviousness-Type Double Patenting

Claims 44-46 and 49-55 further stand rejected under the judicially created doctrine of obviousness-type double patenting as unpatentable over claims 1-17 of U.S. Patent No. 5,942,229. Applicant responds that a terminal disclaimer will be filed when one or more pending claims is in condition for allowance.

Conclusion

All rejections having been addressed, it is respectfully submitted that the present application is in condition for allowance and a Notice to that effect is earnestly solicited. If any points remain in issue, which the examiner feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned attorney at the telephone number listed below.

Respectfully submitted,

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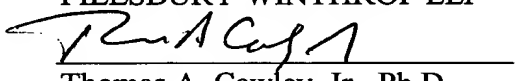

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